Arabian Journal of Chemistry (2019) **12**, 1623–1627

King Saud University

Arabian Journal of Chemistry

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

Design and synthesis of novel pyrazol-3ylthiazoles

Sambandan Yuvaraj, Sreedharannair L. Manju *

Organic Chemistry Division, Vellore Institute of Technology, Katpadi, Vellore 632014, Tamilnadu, India

Received 4 October 2012; accepted 8 October 2014
Available online 16 October 2014

KEYWORDS

Pyrazole;
1,3-Thiazole;
2-Aminothiazole;
Vilsmeier reaction

Abstract Biheterocyclic compounds in recent years have gained a significant importance in medicinal chemistry. In this paper the synthesis of novel pyrazol-3ylthiazoles through Vilsmeier–Haack reaction using 2-amino thiazoles as precursors is described. Synthesis of twelve new derivatives was accomplished with moderate yield (70–76%). Structures of all the newly synthesized compounds were characterized by spectral (^{1}H NMR, ^{13}C NMR, IR, LC–MS) and elemental analyses.

1. Introduction

In the area of heterocyclic chemistry a recent trend has been the revival of interest in biheterocyclic systems. The current interest in these systems may be attributed to their presence as structural units in a variety of highly bioactive terrestrial and marine natural products. It has been recognized that a suitably structured ligand may bind by occupying two or more sites, multivalent, on the biomolecules. This concept has been a new trend in drug research and has been reviewed (Wright and Usher, 2001). Biheterocyclic compounds have also stimulated a keen interest among material chemists, who have been studying polythiophenes and polypyrroles as conducting polymers and oligoheterocycles as molecular wires as well as dyes (Park et al., 2001) with novel optical properties. Biheterocycles having luminescent properties have also been reported (Noack et al., 2002). Some of the biheterocyclic compounds are reported to have much better antibacterial activity when compared to that of monoanalogues (Zhang et al., 1991). Biheterocyclic compounds also can act as a powerful chelating agent, forming stable coordination polymers, complexes with various transition metals and trace elements (Joule et al., 1995; Rout et al., 1996; Thakur et al., 1997; Zhu et al., 2006). Thus need to develop efficient routes to synthesis biheterocycles is very significant.

The 2-aminothiazoles occur widely in structures of pharmaceutical interest together with many natural products (Katritzky et al., 2008) They are used as intermediates in the synthesis of antibacterial, antifungal (Bakr et al., 2012; Gaurav et al., 2006; Ranjana et al., 2011) anticancer (Mei-Jung Lai et al., 2011) and anti-inflammatory activities (Hans, 1977; Wilson et al., 2001; Sharma et al., 1998). Synthetic thiazoles have also been shown a wide variety of biological activity such as antitumour activity (Shao et al., 2006), analgesic (Basavaraja et al., 2008), antimicrobial (Mostafa and Abd El-Salam, 2013; Sharshira and Hamada, 2012), anticonvulsant (Azam et al., 2009), antihelminthic and insecticidal activity (Himaja et al., 2012) as well as applications in liquid crystals and cosmetic sunscreens (Karam et al., 2013). Pyrazoles are another potent moiety that exhibit wide range of pharmacological activities such as antitumour (Nassar, 2010), antimicrobial (Sharshira and Hamada, 2011), anti-inflammatory (Haufel

* Corresponding author. Tel./fax: +91 0416 2241422.
E-mail address: girishmanju@gmail.com (S.L. Manju).
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.arabjc.2014.10.005
1878-5352

and Breitmaier, 1974; Zhai Xin et al., 2006) and anti-hypertensive (Dmytro et al., 2009). So it is very important to synthesize new compounds having both 2-aminothiazole and pyrazole moieties. In this paper we are describing the synthesis of pyrazol-3ylthiazoles using 2-aminothiazoles as precursors. For the pyrazole ring construction among the various methods reported (Gupton et al., 2002; Panda and Jena, 2012; Yahia et al., 2011) we have adopted the Vilsmeier Haack reaction. In this method the hydrazone formed by the reaction of methyl ketone and hydrazine was treated with Vilsmeier Haack complex obtained by the reaction of DMF and phosphorous oxychloride. This method is more advantageous than other methods and the pyrazole ring construction has been achieved in a single step with good yields.

2. Materials and method

IR spectra were recorded in KBr on FT-IR (Research Spectrophotometer Series) and Perkin–Elmer FT-IR (Spectrum 1000). ^{1}H NMR and ^{13}C NMR spectra recorded on a Bruker AMX (400 MHz) Spectrophotometer using DMSO-*d*6, $CDCl_3$ and CD_3OD as solvent. TMS is used as internal standard (chemical shifts in δ) and mass spectra were recorded on a LC–MS instrument. Compounds were checked for their purity by TLC on silica gel G plates and spots were located by UV, iodine vapor and DNP.

*2.1. Synthesis of 1-[4-phenyl-2-(phenylamino)-1,3-thiazol-5-yl]ethanone (**1**)*

To the well stirred solution of the *N*-(phenylcarbamothioyl) benzene carboximidamide (1.0 eq) in methanol and triethylamine (1.5 eq), chloroacetone (1.2 eq) was added and stirred at reflux for overnight. The progress of the reaction was monitored using TLC. On completion of the reaction, the reaction mixture was concentrated to remove methanol and extracted over ethyl acetate and washed with water and dried over sodium sulfate and solvent was recovered in vacuo, and the crude mixture was purified over the column to get compound **1** with 85% yield as a yellow solid, ^{1}H NMR (DMSO-*d*6, 400 MHz) δ (ppm): 1.93(s, 3H, CH_3), 7.01–7.62 (m, 10H, Ar) 10.8 (s, 1H, NH); MS: (M_+), *m*/*z* 294.

*2.2. Synthesis of N-substituted-1-[4-phenyl-2-(phenylamino)-1,3-thiazol-5-yl]ethanone **(2a–c)***

2.2.1. General procedure

To the well stirred solution of compound **1**(1.0 eq) in methanol potassium carbonate (1.5 eq) was added followed by alkyl or benzyl halide (1.2 eq) and the reaction mixture was refluxed for 3 h. On completion of the reaction, the reaction mixture was concentrated to remove the methanol and extracted over ethyl acetate and washed with water and dried over sodium sulfate. The solvent was recovered in vacuo, and the formation of compound was confirmed by NMR and LC–MS.

*2.2.1. 1-{2-[N-methyl(phenyl)amino]-4-phenyl-1,3-thiazol-5-yl}ethanone (**2a**)*

Yellow solid, yield 510 mg (97%). ^{1}H NMR (CD_3OD, 400 MHz, δ): 1.93 (s, 3H, CH_3), 3.5 (s, 3H, CH_3), 7.4–7.56 (m, 10H, Ar); MS: (M_+), *m*/*z* 308.

*2.2.2. 1-{2-[Ethyl(phenyl)amino]-4-phenyl-1,3-thiazol-5-yl}ethanone (**2b**)*

Yellow solid, yield 520 mg (97%). ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 1.26 (t, 3H, CH_3), 1.96 (s, 3H, CH_3), 4.07 (q, 2H, CH_2), 7.27–7.57 (m, 10H, Ar); MS: (M_+), *m*/*z* 322.

*2.2.3. 1-{2-[Benzyl(phenyl)amino]-4-phenyl-1,3-thiazol-5-yl}ethanone (**2c**)*

Yellow solid, yield 600 mg (95%). ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 2.03 (s, 3H, CH_3), 5.22 (s, 2H, CH_2), 7.24–7.60 (m, 15H, Ar); MS: (M_+), *m*/*z* 371.

*2.3. Synthesis of N-substituted N-phenyl-5-[(1E)-1-(2-substituted hydrazinylidene)ethyl]-1,3-thiazol-2-amine (**3a–3l**)*

2.3.1. General procedure

To the well stirred solution of **2a–c** (1.0 eq) in ethanol were added hydrazine (1.0 eq) and catalytic amount of the acetic acid and kept at reflux for 3 h. The reaction was monitored by TLC. On completion of the reaction, the reaction mixture was concentrated under vacuo to remove ethanol and the crude mixture was taken as such for the next step. Some compounds were purified and confirmed by NMR and LC–MS and others **3b**, **3g**, **3h**, and **3l** were confirmed by TLC and taken as such for next step without further purification.

*2.3.1. N-Methyl-N,4-diphenyl-5-[(1E)-1-(2-phenylhydrazinylidene)ethyl]-1,3-thiazol-2-amine (**3a**)*

Yellow solid, yield 245 mg (95%). ^{1}H NMR (DMSO-*d*6, 400 MHz, δ): 1.76 (s, 3H, CH_3), 3.3 (s, 3H, CH_3), 6.69–7.5 (m, 15H, Ar), 9.11 (s, 1H, NH); MS: (M_+), *m*/*z* 398. *Anal*. calcd. for $C_{24}H_{22}N_4S$ (398.52): C, 72.33; H, 5.56; N, 14.06%. Found: C, 72.29; H, 5.61; N, 14.01%.

*2.3.2. N-Methyl-N,4-diphenyl-5-[(1E)-1-(2-(4-Chlorophenyl)hydrazinylidene)ethyl]-1,3-thiazol-2-amine (**3c**)*

Yellow solid, yield 260 mg (93%). ^{1}H NMR (DMSO-*d*6, 400 MHz, δ): 1.76 (s, 3H, CH_3), 3.5 (s, 3H, CH_3), 6.98–7.54 (m, 14H, Ar), 9.2 (s, 1H, NH); MS: (M_+), *m*/*z* 432. *Anal*. calcd. for $C_{24}H_{21}ClN_4S$ (432.97): C, 66.58; H, 4.89; N, 12.94%. Found: C, 66.60; H, 4.85; N, 12.90%.

*2.3.3. N-methyl-N,4-diphenyl-5-[(1E)-1-(2-(2-methyl phenyl)hydrazinylidene)ethyl]-1,3-thiazol-2-amine (**3d**)*

Yellow solid, yield 240 mg (90%). ^{1}H NMR (DMSO-*d*6, 400 MHz, δ): 1.84 (s, 3H, CH_3), 2.1 (s, 3H, CH_3) 3.48 (s, 3H, CH_3), 6.68–7.54 (m, 14H, Ar), 7.8 (s, 1H, NH); MS: (M_+), *m*/*z* 412. *Anal*. calcd. for $C_{25}H_{24}N_4S$ (412.55): C, 72.78; H, 5.86; N, 13.58%. Found: C, 72.70; H, 5.79; N, 13.52% .

*2.3.4. N-Ethyl-N,4-diphenyl-5-[(1E)-1-(2-phenylhydrazinylidene)ethyl]-1,3-thiazol-2-amine (**3e**)*

Yellow solid, yield 243 mg (95%). ^{1}H NMR (DMSO-*d*6, 400 MHz, δ): 1.18 (t, 3H, CH_3), 1.76 (s, 3H, CH_3), 3.99 (q, 2H, CH_2) 6.69–7.5 (m, 15H, Ar), 9.11 (s, 1H, NH); MS: (M_+), *m*/*z* 412. *Anal*. calcd. for $C_{25}H_{24}N_4S$ (412.55): C, 72.78; H, 5.86; N, 13.58%. Found: C, 72.80; H, 5.82; N, 13.61%.

*2.3.5. N-Ethyl-N,4-diphenyl-5-[(1E)-1-(2(4-fluoro phenyl)hydrazinylidene)ethyl]-1,3-thiazol-2-amine (**3f**)*

Yellow solid, yield 253 mg (95%). ^{1}H NMR (DMSO-*d*6, 400 MHz) δ: 1.18 (t, 3H, CH_3), 1.76 (s, 3H, CH_3), 3.99 (q, 2H, CH_2) 6.97–7.9 (m, 14H, Ar), 9.08 (s, 1H, NH); MS: (M_+), *m*/*z* 430. *Anal.* calcd. for $C_{25}H_{23}FN_4S$ (430.54): C, 69.74; H, 5.38; N, 13.01%. Found: C, 69.79; H, 5.32; N, 13.05%.

*2.3.6. N-Benzyl-N,4-diphenyl-5-[(1E)-1-(2-phenylhydrazinylidene)ethyl]-1,3-thiazol-2-amine (**3i**)*

Yellow solid, yield 242 mg (92%). ^{1}H NMR (DMSO-*d*6, 400 MHz, δ): 1.78 (s, 3H, CH_3), 5.2 (s, 2H, CH_2), 6.68–7.51 m, 20H, Ar), 9.11 (s, 1H, NH); MS: (M_+), *m*/*z* 474. *Anal.* calcd. for $C_{30}H_{26}N_4S$ (474.62): C, 75.92; H, 5.52; N, 11.80%. Found: C, 75.89; H, 5.55; N, 11.87%.

*2.3.7. N-Benzyl-N,4-diphenyl-5-[(1E)-1-(2(4-fluorophenyl)hydrazinylidene)ethyl]-1,3-thiazol-2-amine (**3j**)*

Yellow solid, yield 249 mg (93%). ^{1}H NMR (DMSO-*d*6, 400 MHz, δ): 1.78 (s, 3H, CH_3), 5.2 (s, 2H, CH_2), 6.69–7.51 (m, 19H, Ar), 9.11 (s, 1H, NH); MS: (M_+), *m*/*z* 492. *Anal.* calcd. for $C_{30}H_{25}FN_4S$ (492.61): C, 73.15; H, 5.12; N, 11.37%. Found: C, 73.19; H, 5.10; N, 11.31%.

*2.3.8. N-Benzyl-N,4-diphenyl-5-[(1E)-1-(2(4-chloro phenyl)hydrazinylidene)ethyl]-1,3-thiazol-2-amine (**3k**)*

Yellow solid, yield 259 mg (93%). ^{1}H NMR (DMSO-*d*6, 400 MHz, δ): 1.79 (s, 3H, CH_3), 5.2 (s, 2H, CH_2), 6.98–7.52 (m, 19H, Ar), 9.26 (s, 1H, NH); MS: (M_+), *m*/*z* 508. *Anal.* calcd. for $C_{30}H_{25}ClN_4S$ (509.06): C, 70.78; H, 4.95; N, 11.01%. Found: C, 70.72; H, 5.01; N, 11.08%.

*2.4. Synthesis of 3-{substituted 1,3-thiazol-5-yl}-1-substituted 1H-pyrazole-4-carbaldehyde (**4a**–**l**)*

2.4.1. General procedure

To the cooled solution of DMF (8.0 eq) at 0 °C was added $POCl_3$ (3.0 eq) dropwise and stirred at same temperature for another 1 h to form Vilsmeier reagent. Then the compound **3a**–**l** (1.0 eq) was taken in DMF and added drop wise to the reaction mixture for half an hour and stirred at 0 °C for 1 h and then heated at 80 °C for 6 h. Then the reaction mixture was quenched with ice and neutralized with sodium bicarbonate. The resultant solution was then extracted with ethyl acetate, washed with water and dried over sodium sulfate. The solvent was recovered in vacuo and purified over column chromatography. The compound isolated was confirmed by ^{1}H NMR, ^{13}C NMR, mass spectrum and IR spectrum.

*2.4.1. 3-{2-[Methyl(phenyl)amino]-4-phenyl-1,3-thiazol-5-yl}-1-phenyl-1H-pyrazole-4-carbaldehyde (**4a**)*

Yellow solid, yield 164 mg (75%), m.p. 168–169 °C.

IR (KBr, cm^{-1}): 1677(C═O). ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 3.6 (s, 3H, CH_3), 7.2–7.7 (m, 15H, Ar) 8.3 (s, 1H, Ar), 9.2 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$, δ): 119.5, 122.03, 125.32, 127.07, 127.89, 128.52, 128.64, 128.83, 129.41, 129.63, 129.96, 138.81, MS: (M_+), m/z 437. *Anal.* calcd. for $C_{25}H_{20}N_4OS$ (436.53): C, 71.54; H, 4.62; N, 12.83%. Found: C, 71.50; H, 4.66; N, 12.79%.

*2.4.2. 3-{2-[Methyl(phenyl)amino]-4-phenyl-1,3-thiazol-5-yl}-1-(4-fluorophenyl)-1H-pyrazole-4-carbaldehyde (**4b**)*

Yellow solid, yield 159 mg (73%), m.p. 173–174 °C.

IR (KBr, cm^{-1}): 1677 (C═O). ^{1}H NMR ($CDCl_3$, 400 MHz, δ: 3.66 (s, 3H, CH_3), 7.15–7.68 (m, 14H, Ar), 8.3 (s, 1H, Ar) 9.18 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$, δ): 40.15, 116.45, 116.68, 121.35, 121.43, 122.05, 122.34, 127.14, 128.58, 128.69, 128.82, 129.48, 129.99, 145.96, 185.19. MS: (M_+), *m*/*z* 455. *Anal.* calcd. for $C_{26}H_{19}FN_4OS$ (454.52): C, 68.71; H, 4.21; N, 12.33%. Found: C, 68.75; H, 4.25; N, 12.38%.

*2.4.3. 3-{2-[Methyl(phenyl)amino]-4-phenyl-1,3-thiazol-5-yl}-1-(4-chlorophenyl)-1H-pyrazole-4-carbaldehyde (**4c**)*

Yellow solid, yield 159 mg (75%), m.p. 182–183 °C.

IR (KBr, cm^{-1}): 1677(C═O). ^{1}H NMR ($CDCl_3$, 400 MHz, δ: 3.67 (s, 3H, CH_3), 7.27–7.66 (m, 14H, Ar), 8.3 (s, 1H, Ar).9.18 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$, δ: 40.06, 109.13, 120.61, 122.26, 125.33, 127.07, 128.53, 128.66, 128.80, 129.32, 129.75, 129.96, 133.53, 134.65, 137.34, 146.01, 147.74, 150.72, 169.30, 185.07. MS: (M_+), *m*/*z* 471. *Anal.* calcd. for $C_{26}H_{19}ClN_4OS$ (470.97): C, 66.30; H, 4.07; N, 11.90%. Found: C, 66.36; H, 4.11; N, 11.95%.

*2.4.4. 3-{2-[Methyl(phenyl)amino]-4-phenyl-1,3-thiazol-5-yl}-1-(2-methylphenyl)-1H-pyrazole-4-carbaldehyde (**4d**)*

Yellow solid, yield 164 mg (70%), m.p. 143–144 °C.

IR (KBr, cm^{-1}): 1677 (C═O). ^{1}H NMR ($CDCl_3$, 400 MHz, δ: 2.25 (s, 3H, CH_3), 3.65 (s, 3H, CH_3) 7.27–7.66 (m, 14H, Ar), 8.04 (s, 1H, Ar) 9.18 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$, δ: 18.08, 40.21, 109.28, 121.2, 125.2, 125.83, 127.08, 128.45, 128.62, 128.82, 129.44, 129.97, 131.52, 133.49, 133.61, 138.62, 145.96, 169.22, 185.31. MS: (M_+), *m*/*z* 451. *Anal.* calcd. for $C_{27}H_{22}N_4OS$ (450.55): C, 71.98; H, 4.92; N, 12.44%. Found: C, 71.89; H, 4.88; N, 12.40%.

*2.4.5. 3-{2-[Ethyl(phenyl)amino]-4-phenyl-1,3-thiazol-5-yl}-1-phenyl-1H-pyrazole-4-carbaldehyde (**4e**)*

Yellow solid, yield 164 mg (70%), m.p. 171–172 °C. IR (KBr, cm^{-1}): 1676 (C═O). ^{1}H NMR ($CDCl_3$, 400 MHz, δ: 1.34 (t, 3H, CH_3), 4.1 (q, 2H, CH_2), 7.2–7.7 (m, 15H, Ar), 8.36 (s, 1H, Ar), 9.21 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$, δ: 13.25, 47.4, 108.91, 119.48, 121.95, 127.35, 127.74, 127.85, 128.42, 128.62, 128.81, 129.34, 129.62, 130.13, 138.81, 144.40, 147.71, 169.25, 185.40. MS: (M_+), *m*/*z* 451. *Anal.* calcd. for $C_{27}H_{22}N_4OS$ (450.55): C, 71.98; H, 4.92; N, 12.44%. Found: C, 71.91; H, 4.89; N, 12.49% .

*2.4.6. 3-{2-[Ethyl(phenyl)amino]-4-phenyl-1,3-thiazol-5-yl}-1-(4-fluorophenyl)-1H-pyrazole-4-carbaldehyde (**4f**)*

Yellow solid, yield 165 mg (73%), m.p. 185–186 °C.

IR (KBr, cm^{-1}): 1676 (C═O). ^{1}H NMR ($CDCl_3$, 400 MHz, δ: 1.33 (t, 3H, CH_3), 4.1 (q, 2H, CH_2), 7.14–7.68(m, 14H, Ar), 8.2 (s, 1H, Ar), 9.19 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$, δ: 13.17, 47.43, 108.67, 116.34, 116.57, 121.25, 1 21.33, 121.95, 127.27, 127.76, 128.45, 128.56, 128.76, 129.34, 130.09, 135.08, 144.24, 163.03, 169.21, 185.18. MS: (M_+), *m*/*z* 469. *Anal.* calcd. for $C_{27}H_{21}FN_4OS$ (468.55): C, 69.21; H, 4.52; N, 11.96%. Found: C, 69.28; H, 4.57; N, 11.90% .

*2.4.7. 3-{2-[Ethyl(phenyl)amino]-4-phenyl-1,3-thiazol-5-yl}-1-(4-chlorophenyl)-1H-pyrazole-4-carbaldehyde (**4g**)*

Yellow solid, yield 165 mg (76%), m.p. 200–201 °C.

IR (KBr, cm^{-1}): 1677 (C═O). ^1H NMR ($CDCl_3$, 400 MHz, δ: 1.33 (t, 3H, CH_3) 4.14 (q, 2H, CH_2), 7.27–7.65 (m, 14H, Ar), 8.32 (s, 1H, Ar), 9.19 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$, δ: 13.24, 47.48, 120.59, 122.14, 127.37, 127.86, 128.55, 128.83, 129.30, 129.75, 130.18, 133.49, 137.31, 144.32, 169.33, 185.24. MS: (M_+), *m/z* 485. *Anal.* calcd. for $C_{27}H_{21}ClN_4OS$ (485): C, 66.86; H, 4.36; N, 11.55%. Found: C, 66.80; H, 4.40; N, 11.50%.

*2.4.8. 3-{2-[Ethyl(phenyl)amino]-4-phenyl-1,3-thiazol-5-yl}-1-(2-methylphenyl)-1H-pyrazole-4-carbaldehyde (**4h**)*

Yellow solid, yield 157 mg (72%), m.p. 145–146 °C.

IR (KBr, cm^{-1}): 1677 (C═O). ^1H NMR ($CDCl_3$, 400 MHz, δ: 1.33 (t, 3H, CH_3), 2.24(s, 3H, CH_3), 4.15(q, 2H, CH_2), 7.27–7.66 (m, 14H, Ar), 8.03 (s, 1H, Ar), 9.28 (s, 1H, CHO), ^{13}C NMR ($CDCl_3$, δ: 13.17, 18.01, 121.15, 125.76, 126.75, 127.23, 127.65, 128.74, 129.33, 130.05, 131.43, 133.45, 138.58, 185.36. MS: (M_+), *m/z* 465. *Anal.* calcd. for $C_{28}H_{24}N_4OS$ (464.58): C, 72.39; H, 5.21; N, 12.06%. Found: C, 72.41; H, 5.28; N, 12.11%.

*2.4.9. 3-{2-[Benzyl(phenyl)amino]-4-phenyl-1,3-thiazol-5-yl}-1-phenyl-1H-pyrazole-4-carbaldehyde (**4i**)*

Yellow solid, yield 162 mg (75%), m.p. 142–143 °C. IR (KBr, cm^{-1}): 1681 (C═O) cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ): 5.31 (s, 2H, CH_2), 7.27–7.70 (m, 20H, Ar), 8.37 (s, 1H, Ar), 9.20 (s, 1H, CHO), ^{13}C NMR ($CDCl_3$, δ): 56.18, 109.29, 116.44, 116.67, 121.33, 121.43, 122.04, 127.07, 127.50, 127.79, 128.46, 128.59, 128.64, 129.50, 130.07, 134.42, 135.09, 137.36, 144.43, 147.57, 150.17, 169.56, 185.23. MS: (M_+), *m/z* 513. *Anal.* calcd. for $C_{32}H_{24}N_4OS$ (512.62): C, 74.98; H, 4.72; N, 10.93%. Found: C, 74.93; H, 4.69; N, 10.97%.

*2.4.10. 3-{2-[Benzyl(phenyl)amino]-4-phenyl-1,3-thiazol-5-yl}-1-(4-fluorophenyl)-1H-pyrazole-4-carbaldehyde (**4j**)*

Yellow solid, yield 157 mg (73%), m.p. 156–157 °C. IR (KBr, cm^{-1}): 1677 (C═O) cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ): 5.31 (s, 2H, CH_2), 7.16–7.67 (m, 19H, Ar), 8.30 (s, 1H, Ar), 9.20 (s, 1H, CHO), ^{13}C NMR ($CDCl_3$, δ): 56.18, 109.29, 116.44, 116.67, 121.33, 121.43, 122.04, 127.07, 127.50, 127.79, 128.46, 128.59, 128.64, 129.50, 130.07, 134.42, 135.09, 137.36, 144.43, 147.57, 150.17, 169.56, 185.23, MS: (M_+), *m/z* 532. Anal. calcd. For $C_{32}H_{23}FN_4OS$ (530.61): C, 72.43; H, 4.37; N, 10.56%. Found: C, 72.39; H, 4.30; N, 10.59%.

*2.4.11. 3-{2-[Benzyl(phenyl)amino]-4-phenyl-1,3-thiazol-5-yl}-1-(4-chlorophenyl)-1H-pyrazole-4-carbaldehyde (**4k**)*

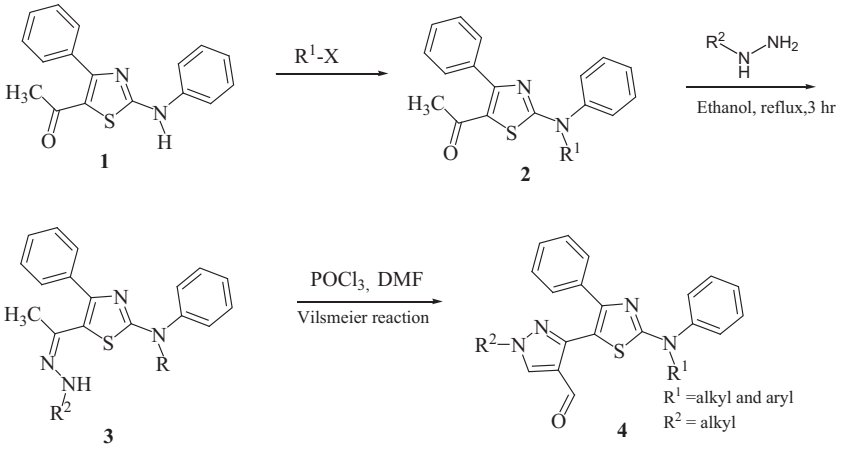
Yellow solid, yield 154 mg (72%), m.p. 184–185 °C. IR (KBr, cm^{-1}): 1677 (C═O) cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 5.31 (s, 2H, CH_2), 7.26–7.65 (m, 19H, Ar), 8.33 (s, 1H, Ar), 9.19 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$ δ): 56.29, 109.23, 120.59, 122.17, 127.08, 127.52, 127.85, 128.47, 128.50, 128.66, 128.85, 129.39, 129.77, 130.10, 133.55, 134.32, 137.27, 137.31, 144.39, 147.62, 169.61, 185.14. MS: (M_+), *m/z* 547. *Anal.* calcd. for $C_{32}H_{23}ClN_4OS$ (547.07): C, 70.25; H, 4.24; N, 10.24%. Found: C, 70.19; H, 4.20; N, 10.19%.

*2.4.12. 3-{2-[Benzyl(phenyl)amino]-4-phenyl-1,3-thiazol-5-yl}-1-(2-methylphenyl)-1H-pyrazole-4-carbaldehyde (**4l**)*

Yellow solid, yield 162 mg (75%), m.p. 139–141 °C. IR (KBr, cm^{-1}): 1677 (C═O) cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, δ): 2.24 (s, 2H, CH_3), 5.30 (s, 2H, CH_2), 7.26–7.66 (m, 19H, Ar), 8.04 (s, 1H, Ar), 9.3 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$, δ): 18.03, 56.13, 109.40, 121.35, 125.82, 126.81, 126.95, 127.40, 127.55, 128.30, 128.40, 128.42, 128.51, 128.76, 129.36, 129.96, 131.49, 133.47, 133.53, 134.78, 137.55, 138.66, 144.58, 147.11, 150.18, 169.42, 185.34. MS: (M_+), *m/z* 527. *Anal. calcd.* For $C_{33}H_{26}N_4OS$ (526.65): C, 75.26; H, 4.98; N, 10.64%. Found: C, 75.29; H, 4.91; N, 10.69%.

3. Results and discussion

The starting material, 2-aminothiazoles has been synthesized by reported methods. Among the various synthetic methods used for the construction of the 1,3-thiazole rings (Ruettinger, 1976; Ortega et al., 2000), the strategy involving benzamidine and phenylisothiocyanate as starting material (Murawewa, 1959) was adopted in the present investigation. The treatment of the benzamidine and phenylisothiocyanate



Scheme 1 General synthetic pathways for the preparation of synthesis of 3-{substituted 1,3-thiazol-5-yl}-1-substituted 1*H*-pyrazole-4-carbaldehyde.

Table 1 Synthesis of 3-{substituted 1,3-thiazol-5-yl}-1-substituted 1*H*-pyrazole-4-carbaldehydes.

Entry	Compound	R^1	R^2	Yield (%)
1	**4a**	CH_3	C_6H_5	75
2	**4b**	CH_3	4-F-C_6H_5	73
3	**4c**	CH_3	4-Cl-C_6H_5	75
4	**4d**	CH_3	2-CH_3-C_6H_5	70
5	**4e**	C_2H_5	C_6H_5	70
6	**4f**	C_2H_5	4-F-C_6H_5	73
7	**4g**	C_2H_5	4-Cl-C_6H_5	76
8	**4h**	C_2H_5	2-CH_3-C_6H_5	72
9	**4i**	$C_6H_5CH_2$	C_6H_5	75
10	**4j**	$C_6H_5CH_2$	4-F-C_6H_5	73
11	**4k**	$C_6H_5CH_2$	4-Cl-C_6H_5	72
12	**4l**	$C_6H_5CH_2$	2-CH_3-C_6H_5	75

with diisopropylethylamine in DMF yielded *N*-(phenylcarbamothioyl)benzene carboximidamide. This on treatment with chloroacetone and triethylamine in methanol yielded a mixture of [2-(*N*-benzyl-*N*-ethylamino)-4-methylthiazol-5-yl)(phenyl)methanone (major product) and 1-[2-(*N*-benzyl-*N*-ethylamino-4-phenylthiazol-5-yl)ethanone **1** (minor product), the isolation of the two products was difficult since both have same *Rf* value (TLC). The mixture was then treated with alkyl halides with potassium carbonate as base in methanol at reflux conditions to yield N-substituted-1-[4-phenyl-2-(phenylamino)-1,3-thiazol-5-yl]ethanone **2a**–**c**. This was then treated with different hydrazines. The minor compound only reacted with hydrazine and converted to hydrazones **3a**–**l**. Among these compounds, **3b**, **3g**, **3h**, and **3l** were highly unstable at room temperature and they were taken directly into the next step without further purification Scheme 1. All other compounds were column chromatographed and were confirmed by spectral studies. The hydrazone **3a** treated with phosphorous oxychloride in DMF under Vilsmeier–Haack condition (Meth-Cohn and Stanforth, 1991) afforded a yellow compound **4a** which was purified through column chromatography. The appearance of the band at 1680.8 cm^{-1} in the IR spectrum of the compound **4a** indicated the presence of a carbonyl group. The NMR spectrum showed a singlet at around δ 8.3 ppm corresponding to the pyrazole ring which confirmed the cyclization and also disappearance of the methyl proton at around δ 1.9 ppm was observed. The formation of the compound was then confirmed by the mass spectral analysis. It exhibited a molecular ion peak at m/z 436 corresponding to its molecular weight. Thus the compound obtained has been confirmed as 3-{2-[methyl(phenyl)amino]-4-phenyl-1,3-thiazol-5-yl}-1-phenyl-1*H*-pyrazole-4 carbaldehyde. Similarly all the other derivatives were synthesized, column chromatographed and characterized by spectroscopic studies. The yields of the compounds are found to be the same irrespective of the substituent at the R2 position (Table 1).

4. Conclusions

In summary we have described an efficient synthetic route to obtain novel pyrazol-3ylthiazoles starting from 2-aminothiazoles. The generality of the method has been demonstrated by synthesizing 12 derivatives.

References

Azam, F., Ikskas, I.A., Khokra, S.L., Prakash, O., 2009. Eur. J. Med. Chem. 44, 203–211.

Basavaraja, K.M., Somasekhar, B., Appalaraju, S., 2008. Ind. J. Heterocycl. Chem. 18, 69–72.

Bakr, F., Abdel-Wahab, Ehab Abdel-Latif, Hanan, A., Mohamed, Ghada, E.A., Awad, 2012. Eur. J. Med. Chem. 52, 263–268.

Dmytro, H., Borys, Z., Olexandr, V., Lucjusz, Z., Andrzej, G., Roman, L., 2009. Eur. J. Med. Chem. 44, 1396–1404.

Gaurav, G., Suvarna, G., Kini, 2006. Eur. J. Med. Chem. 41, 256–262.

Gupton, T., Clough, C., Miller, B., Norwood, K., Hickenboth, R., Chertudi, Itta Bluhn, Cutro, R., Petrich, A., Hicks, A., Wilkinson, R., Sikorski, A., 2002. Tetrahedron 58, 5467–5474.

Hans, N.; Swiss Patent 592103, 1977, 1978. Chem. Abstr. 88, 22886.

Haufel, J., Breitmaier, E., 1974. Angew. Chem. 13, 604.

Himaja, M., Gupta, N., Munirajashekhar, D., Karigar, A., Sikarwar, M.K., 2012. J. Pharm. Sci. Innov. 14, 33–36.

Joule, J.A., Nills, K., Smith, G.F., 1995. Heterocyclic Chemistry, 3rd edn. Chapman and Hall, London.

Karam, H., Tomma, H., Al-Dujaili, H., 2013. Chem. Mater. Res. 3, 162–171.

Katritzky, A.R., Ramsden, C.A., Scriven, E.F.V., Taylor, R.J.K. (Eds.), 2008. Comprehensive Heterocyclic Chemistry. Elsevier: Inc., Oxford, pp. 635–754, Vol. 4.

Lai, Mei-Jung, Chang, Jang -Yang, Lee, Hsueh -Yun, Kuo, Ching -Chuan, Lin, Mei -Hsiang, Hsieh, Hsing -Pang, Chang, Chi -Yen, Jian-Sung, Wu, Su-Ying, Wu, Shey, Kuang-Shing, Liou, Jing-Ping, 2011. Eur. J. Med. Chem. 46, 3623–3629.

Meth-Cohn, O., Stanforth, S.P., 1991. Comp. Org. Synth. 2, 777–794.

Mostafa, M.S., Abd El-Salam, N.M., 2013. Der. Pharm. Chem. 5, 1–7.

Murawewa, D.A.N.K.A.S., 1959. Dokl. Akad. Nauk SSSR 126, 1274.

Nassar, E., 2010. J. Am. Sci 6, 463–471.

Panda, Niranjan., Jena, Ashis Kumar, 2012. J. Org. Chem. 77, 9401–9406.

Noack, A., Schroder, A., Hartmann, H., 2002. Dyes Pigm. 57, 131.

Ortega, R., Aviles, A., Cruz, A., Gómez, R., Plata, A., 2000. J. Org. Chem. 65, 7244.

Park, J.W., Lee, J.H., Kha, S.I., Kim, T.W., 2001. Curr. Appl. Phys. 1, 125.

Ranjana, A., Rajiv, K., Sunil, K., Gaurav, G., Ritu, M., Jitender, S., 2011. J. Fluorine Chem. 132, 965–972.

Rout, K.C., Mohanty, R.R., Jena, S., Dash, K.C., 1996. Polyhedron 15, 1023.

Ruettinger, PHARAT; 1976. Pharmazie: German, 31, 218.

Shao, L., Zhou, X., Hu, Y., Jin, Z., Liu, J., Fang, J.X., 2006. Metal-Org. Nano-Metal Chem. 36, 325–330.

Sharma, P.K., Swonhney, S.N., Gupta, A., Singh, G.B., Bani, S., 1998. Indian J. Chem. 37B, 371.

Sharshira, E.M., Hamada, N.M.M., 2011. Molecules 16, 2304–2312.

Sharshira, E.M., Hamada, N.M.M., 2012. Am. J. Org. Chem. 2, 69–73.

Thakur, P., Chakarvortty, V., Dash, K.C., 1997. Polyhedron 16, 1417.

Wilson, K.J., Utig, C.R., Subhasinghe, N., Hoffman, J.B., Rudolph, N.J., Soll, R., Molloy, C.J., Bone, R., Green, D., Randall, J., 2001. Bioorg. Med. Chem. Lett. 11, 915.

Wright, D., Usher, L., 2001. Curr. Org. chem. 5, 1107.

Yahia, Nasser Mabkhot, Abdullah, Mohammad Al-Majid, Alamary, S., 2011. Molecules 16, 7706–7714.

Zhai Xin, Zhao Yan Fang, Wang Jia, Hong Wei, Huang Liang, Gong Ping, 2006. Chem. Res. Chin. 22 (4), 4594.

Zhang, Z.Y., Chen, X., Wei, L.L., Ma, Z.L., 1991. Chem. Res. Chin. Univ. 2, 129.

Zhu, X., Zhang, Y.M., Li, B.L., Zhang, Y., 2006. J. Coord. Chem. 59, 513.